

Die Rolle der Umwelt bei der Entstehung der caninen atopischen Dermatitis

Abstract

Canine and human atopic dermatitis (AD) are multifaceted diseases which clinical development may be influenced by several factors such as genetic background, environment, secondary infections, food and psychological effects. The role of the environment has been extensively examined in humans but remains unclear in dogs. The aim of the present study is to examine environmental factors in 2 genetically close breeds: Labrador and Golden Retrievers. Using standard criteria, atopic dogs were selected and compared to healthy individuals. Information on environmental factors was collected using a questionnaire. Univariate and multivariable logistic regression was subsequently used in order to assess the association between all potential risk factors and the disease status. The following parameters, resulting from the multivariable logistic regression, were associated with an increased risk of disease development: living in a shed during puppyhood, adoption at the age of 8 to 12 weeks and washing the dog regularly. On the contrary, the following factors were associated with a lower risk: living in a rural environment, living in a household with other animals and walking in the forest. These associations do not prove causality but support the primary hypothesis that certain environmental factors may influence canine AD development. Further studies are warranted to confirm the current results and conclusions.

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Role of the environment in the development of canine atopic dermatitis

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Role of the environment in the development of canine atopic dermatitis in Labrador and Golden Retrievers

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Abstract

Canine and human atopic dermatitis (AD) are multifaceted diseases which clinical development may be influenced by several factors such as genetic background, environment, secondary infections, food and psychological effects. The role of the environment has been extensively examined in humans but remains unclear in dogs.

The aim of the present study is to examine environmental factors in 2 genetically close breeds: Labrador and Golden Retrievers. Using standard criteria, atopic dogs were selected and compared to healthy individuals. Information on environmental factors was collected using a questionnaire. Univariate and multivariable logistic regression was subsequently used in order to assess the association between all potential risk factors and the disease status.

The following parameters, resulting from the multivariable logistic regression, were associated with an increased risk of disease development: living in a shed during puppyhood, adoption at the age of 8 to 12 weeks and washing the dog regularly. On the contrary, the following factors were associated with a lower risk: living in a rural environment, living in a household with other animals and walking in the forest. These associations do not prove causality but support the primary hypothesis that certain environmental factors may influence canine AD development. Further studies are warranted to confirm the current results and conclusions.

Introduction

Canine atopic dermatitis (CAD) is a genetically-predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated most commonly with IgE antibodies produced in response to environmental allergens.¹

CAD, which on average affects 10-15% of the canine population, has become more frequent during the past decades.^{2,3} Such a sudden and drastic increase suggests that environmental factors, in addition to genetic factors, play a role in the development of the disease.⁴

Recent studies have demonstrated that canine AD bears numerous similarities to its human counterpart such as prevalence, development, clinical and histological signs, immunological mechanisms and response to treatment.⁵

Human AD is regarded as a multifaceted disease resulting from complex interactions between host (genetic susceptibility leading to skin barrier or immunologic dysfunction) and environmental factors (exposure to aero- or food allergens, contact with infectious agents, stress, UV light).⁶

Environmental factors influencing development of human atopic dermatitis (HAD) have been extensively studied and some of them may be relevant for dogs. As pets have accompanied human beings in their lifestyle changes, it is tempting to hypothesize that shared environmental factors may have influenced the development of CAD. The so-called "hygiene hypothesis" suggests that early life exposures to microbes can influence the development of the immune system, may promote Th1 responses and down-regulate Th2 responses.⁴ Therefore, one can speculate that the increased use of antibiotics, vaccines and deworming drugs in dogs may have contributed to the increasing prevalence of CAD. It has been shown that both living in an urban area and a Western lifestyle tend to increase the risk of developing allergic diseases in humans.⁷ Exposure to diesel exhaust particles, for example, has also been associated with increased incidence of HAD.⁶

Contact with farm animals seems to have a protective effect on the development of HAD by early exposure to bacterial endotoxins, which are potent inducers of type Th1 cytokines.⁸ Furthermore, contact with dogs appears to have a protective effect on children.⁶ The age of the individuals at the time of exposure to different allergens has also been shown to play an important role.⁸ Finally, diets rich in essential fatty acids have been associated with a decreased risk of developing the signs of the disease.⁹ In comparison, data in the veterinary literature is very limited. A study carried out in Sweden suggests that living in a town and being born in autumn is associated with an increased risk of CAD development.¹⁰ Another study carried out by the same team reveals that home-made food diets during pregnancy seems to have a protective effect on the development of AD in puppies.¹¹

The goal of this study was to analyse the environmental risk factors for CAD in Swiss and German Labrador and Golden Retrievers.

Material and methods

The present work was done in the context of a larger study with the aim of evaluating genetic factors that influence the development of CAD in Labrador and Golden Retrievers. This LUPA project is a European initiative aiming at collecting DNA samples from large cohorts of dogs suffering from diseases relevant to human health (The LUPA Project: <http://www.eurolupa.org>). Canine atopic dermatitis (CAD) is one of the diseases chosen because of its similarities with human atopic dermatitis. For the genetic study, dogs of these two breeds and also crossbreeds (Labrador x Golden Retriever) were chosen in Switzerland and Germany between January 2008 and October 2009. Cases and controls provided by animal hospitals in Zurich and Bern as well as dogs referred by dermatologists in Switzerland and Germany, Retriever Clubs and guide dog organizations in Switzerland were included. For each dog (older than month), a thorough history was recorded and a clinical examination was performed by a veterinary dermatologist in order to determine if it was allergic or not: In a first step, all dogs with a history of skin or ear diseases not compatible with atopic dermatitis were excluded and dogs without any present or past signs of skin/ear diseases were enrolled in the control group. For dogs with suspected CAD, Willemse¹² and Prélud¹³ criteria were used and resembling diseases such as ectoparasites, primary bacterial and yeasts infections were ruled out. Most dogs were submitted to a six-week elimination diet and a subsequent diet challenge. None of these dogs responded completely to this procedure and could be consequently considered food allergic. Following the recent position of the International Task Force on atopic dermatitis¹⁴ stating that food allergens might in some individuals trigger flares of CAD, dogs presenting clinical signs of CAD were kept in the CAD group. Dog owners were asked to fill in a questionnaire of 46 questions clustered in five risk factor groups encompassing the following aspects of the dog's lifestyle (see appendix): date of birth, breeding conditions, surroundings, housing conditions and feeding. When the answer "others" was ticked by the owners, the answer was not taken into account for further statistical analysis.

When questions corresponded to more than one risk factor, they were either interpreted as yes/no (example: Question: Are there other animals in the surrounding area? Possible answers in the questionnaire: no, dogs/cats, birds, ruminants, horses, rodents (including rabbits) or others; for the statistical analysis: Are there dogs and cats in the surrounding area? yes/no; Are there birds in the surrounding area? yes/no, and so on) or grouped together (example: Question: In which residential area does the owner live with the dog? Possible answers: Rural, urban, both (rural and urban) or suburban; for the statistical analysis we grouped rural and both together as rural and urban and suburban together as urban).

After initial descriptive statistics and data cleaning a basic two factor logistic regression model was run to assess the association between all risk factors (individually) and disease status (dogs with CAD versus healthy control dogs). Breed was always included as a potential confounder. Association between the month of birth (12 categories) and disease status was analysed with a cross tabulation and 2-sided Fishers Exact test. Significance was set at a p-value of < 0.05 . However, trends with a p-value < 0.12 were taken into account when they had a relation to other results associated with p-value lower than 0.05.

Risk factors were considered as candidates for the final multivariable analysis if at least one of the risk factors in the group had a p-value < 0.12 (Table 2). In order to avoid problems with collinearity in the final model, the association between candidate

risk factors was assessed within topic groups: (a) breeding conditions, (b) surroundings, (c) housing conditions and (d) feeding using a cross tabulation and chi-square test. Factors within those groups that were significantly associated were either combined or one was excluded from further analysis (Table 2).

All remaining candidates were offered to an automatic forward selection process for the multivariable logistic regression analysis until 10 variables (including intercept) were selected in decreasing order of significance. Subsequently, non-significant variables ($p\text{-value} < 0.05$) were manually inserted / added in a stepwise elimination process. Finally, breed was forced into the model to correct for any potential confounding effect and the parameter estimates of those factors remaining in the final model expressed as odds ratios and 95% confidence intervals. All descriptive and conclusive statistical data analyses were performed with NCSS 2007 (NCSS, Kaysville, Utah, USA).

Results

Data from 515 dogs was collected for the initial genetic study. Crossbreed dogs ($n = 12$) as well as dogs with non-allergic dermatological problems ($n = 125$) were not taken into account for the present study. Data for 378 dogs, including 224 Labrador Retrievers (59.3%) and 154 Golden Retrievers (40.7%) was consequently analyzed in this work. Thereof, 144 dogs (38.1%) suffered from atopic dermatitis whereas 234 (61.9%) were classified as control dogs.

For the univariate analysis procedure we ensured first that breed (Labrador versus Golden Retriever) did not influence the outcome of the analysis. In all variable-screening steps, the breed was non-significant with odds ratios ranging from 0.658 to 0.933, thus indicating that in this data set there was no significant association between breed (Labrador versus Golden Retriever) and CAD.

Results of the first step analysis (univariate analysis) are shown in Table 1 and Table 2. This analysis suggests that 31 factors might play a protective or risk factor with regard to the development of CAD. These factors were submitted to the selection process described above and 10 risk factors were elected for multivariate analysis. Statistically significant results of the multivariable logistic regression are summarized in Table 3, 6 factors presenting a p -value <0.05 .

Date of birth

The first risk factor group was the date of birth. In the multivariate analysis, only the comparison between warm seasons (spring/summer, months 3 to 8) and cold months (autumn/ winter, months 9 to 2) was taken into account. However, this factor was not associated with a significant higher or lower risk for the development of the disease in the multivariate analysis.

Breeding conditions

In the risk factors group "breeding conditions", 7 factors were significantly associated with the disease in the univariate analysis. Three of them were selected for the multivariate analysis, two of them presenting a significant association with CAD. Puppies kept in a shed outside of the breeder's house during puppyhood developed CAD more often (OR 19.6) than dogs kept indoors during the first months of life (p -value 0.006).

Furthermore, dogs adopted between the age of 8 to 12 weeks developed CAD more often (OR 4.89; p -value 0.011) than dogs adopted at an age of less than 8 weeks.

Surrounding area

In this group of risk factors, 7 factors were pre-selected by applying the univariate analysis. As some of them correlate strongly with each other, only three factors were selected for multivariate analysis.

Firstly, we compared the proportions of atopic dogs living in an urban or rural environment in both groups. This analysis revealed that dogs living in urban environments developed CAD more often (OR 2.67) than dogs living in the countryside (p -value 0.002).

It also became apparent that walking the dog regularly in a forest causes a significantly lower probability (p -value 0.006) of developing CAD (OR 0.41).

Housing conditions

Among the 13 risk factors preselected with the univariate analysis, eight of them were selected for the second step and two of them showed significant association with CAD.

Whereas the presence of other animals (dogs and cats) in the same household had a protective effect, dogs living alone (p-value 0.020) were affected more often (OR 1.95).

Shampooing may also influence the disease. In fact, dogs that were washed once per week (p-value 0.011) by the owner presented CAD more often (OR 21.47) than dogs that were washed never or less than once per week.

In the multivariate analysis feeding-related factors did not reveal an influence on the development of the disease.

Possible interactions were not tested due to the limited number of observations in the final model.

Discussion

To the best of our knowledge, the present study is the third one aiming at exploring the role of environmental factors in the development of CAD. The first study was based on insured dogs in Sweden and compared the living environment of atopic and non-atopic animals.¹⁰ The study had the advantage of enrolling a large number of animals. However, the disadvantage was that the diagnoses were poorly controlled. The second study was case-controlled and included only three breeds.¹¹ A further advantage of this second study was that not only the owners but also the breeders were asked to fill in the questionnaire. However, the major drawback of this second study was the limited number of included dogs (n: 119).

In comparison, the study presented in this paper was slightly different since it concentrated on two genetically close breeds in a limited geographical area only and enrolled numerous animals using only the owners' questionnaires. These differences are to be taken into account when comparing the results.

Epidemiological studies consist of computing odds ratios and determining whether differences are statistically significant or not. It should be kept in mind that differences may be directly associated to the factors studied, but are sometimes also linked to interacting or confounding factors. For example, we demonstrated that living in a city is associated with an increased expression of the clinical signs of CAD. This could be due to exposure to diesel exhaust particles (like in human beings), the lack of contact with microbes or other factors. In this study, confounding or interacting factors could include boredom (because dogs living in the city usually spend less time outside) or the fact that owners living in a city take their pets to veterinarians more frequently, which results in an increased diagnosis of AD. In the following discussion, we consider these as potential interacting factors.

Walking the dog regularly in a forest and living in a rural area have a protective effect in the development of CAD in the Labrador and Golden Retrievers included in this study. It is tempting to interpret this association in the light of some human studies suggesting that the urban lifestyle may favour the development of AD.¹⁵ However, as mentioned previously some factors that are specific to the canine way of life may also influence these outcomes.

The breeding conditions were also shown to play an important role in the development of CAD.

Puppies living outdoors in a shed have a significantly higher incidence of developing AD than puppies living in a house during the first month of their life. This result could be regarded as surprising because indoor dogs are more exposed to house dust mites allergens, which are supposed to play a major role in CAD but may be explained by an increased exposure to infectious agents, leading, for example, to diarrhoea and skin infections. These latter diseases may contribute to an increase in exposure to allergens and alteration of the epidermal barrier. Our findings seem to contradict the preliminary findings on the protective effect of endoparasites in dogs with CAD.¹⁶ However, these dogs had already been suffering from CAD. Therefore, a possible protective preventive effect on developing CAD in dogs cannot be evaluated. Moreover, the importance of regular deworming pets in preventing zoonosis cannot be overlooked.

Dogs that were adopted from the new owner at an age between 8 to 12 weeks have a higher risk of developing CAD than dogs adopted at an age of less than 8 weeks. 8 to 12 weeks is the normal age a puppy changes hands and at this age one cannot yet diagnose an allergic disease. This period may correspond to a pivotal phase of the development of the immune system and the exposure or absence of exposure to certain allergens during this period may be crucial for the development of CAD.

Dogs living together with other dogs or with cats less often showed CAD than dogs living alone. Similar findings were revealed in humans which may support the hygiene hypothesis.⁶ One confounding factor could be that the owners of atopic dogs usually do not adopt other animals.

Washing the dog once per week or more is strongly correlated with the development of CAD. This correlation derives most certainly from the fact that washing the dog is an element of the normal treatment of allergic dogs.

This study provides an overview of the possible risk factors associated with CAD. Some results such as living in a rural area are consistent with results found concerning humans or from veterinary literature. However, this study was carried out in one specific geographical area and only encompassing dogs from two breeds. This may have influenced the results of the study.

Similar studies carried out in other countries or with other dog populations are warranted to confirm or refute the results of the present one.

Ideally, cohort studies studying the influence of specific controlled factors on the development of the diseases should be carried out in the future.

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References

1. Olivry T, DeBoer DJ, Griffin CE et al. The ACVD task force on canine atopic dermatitis: forewords and lexicon. *Veterinary Immunology and Immunopathology* 2001; 81: 143-6.
2. Halliwell RE. Atopic disease in the dog. *Veterinary Record* 1971; 89: 209-14.
3. DeBoer DJ. Survey of intradermal skin testing practices in North America. *Journal of the American Veterinary Medicine Association* 1989; 195: 1357-63.
4. Naleway AL. Asthma and atopy in rural children: is farming protective? *Clinical Medicine & Research* 2004; 2: 5-12.
5. Marcella R, Girolomoni G. Canine models of atopic dermatitis: a useful tool with untapped potential. *The Journal of Investigative Dermatology* 2009; 129: 2351-7.
6. Biagini Myers JM, Wang N, LeMasters GK et al. Genetic and environmental risk factors for childhood eczema development and allergic sensitization in the CCAAPS cohort. *Journal of Investigative Dermatology* 2010; 130: 430-7.
7. Grammatikos AP. The genetic and environmental basis of atopic diseases. *Annals of Medicine* 2008; 40: 482-95.
8. Torres-Borrego J, Molina-Teran AB, Montes-Mendoza C. Prevalence and associated factors of allergic rhinitis and atopic dermatitis in children. *Allergologia et Immunopathologia* 2008; 36: 90-100.
9. Trak-Fellermeier MA, Brasche S, Winkler G et al. Food and fatty acid intake and atopic disease in adults. *The European Respiratory Journal* 2004; 23: 575-82.
10. Nodtvedt A, Egenvall A, Bergvall K et al. Incidence of and risk factors for atopic dermatitis in a Swedish population of insured dogs. *Veterinary Record* 2006; 159: 241-6.
11. Nodtvedt A, Bergvall K, Sallander M et al. A case-control study of risk factors for canine atopic dermatitis among boxer, bullterrier and West Highland white terrier dogs in Sweden. *Veterinary Dermatology* 2007; 18: 309-15.
12. Willemse T. Atopic skin disease: a review and reconsideration of diagnostic criteria. *Journal of Small Animal Practice* 1986; 27: 771-8.
13. Prélard P, Guaguère E, Alhaidari Z et al. Reevaluation of diagnostic criteria of canine atopic dermatitis. *Revue de Medecine Veterinaire* 1998; 154: 1057-64.
14. Olivry T,. Food for thought: pondering the relationship between canine atopic dermatitis and cutaneous adverse food reactions . *Veterinary Dermatology* 2007; 18: 390-91.
15. Ciaccio CE, Portnoy JM. Strategies for primary prevention of atopy in children. *Current Allergy and Asthma Reports* 2008; 8: 493-9.

16. Helmer M, Epe C, Mueller RS. The effect of helminth administration on canine atopic dermatitis - a pilot study. *Veterinary Dermatology* 2008; 19: 1-83

Figures

Table1:

Association between month of birth and disease status. P-values < 0.05 (2-sided Fishers Exact test) indicate statistically significant differences between that month and all others combined. There is a significant result in month 8 and month 10.

Month of birth	Season	No. dogs	No. pos (%)	p-value
1	winter	28	13 (46.4)	0.426
2	winter	26	12 (46.2)	0.533
3	spring	37	13 (35.1)	0.724
4	spring	40	18 (45)	0.494
5	spring	33	12 (36.4)	0.853
6	summer	42	13 (31)	0.315
7	summer	44	17 (38.6)	1.000
8	summer	22	4 (18.2)	0.043
9	autumn	32	12 (37.5)	1.000
10	autumn	30	18 (60)	0.019
11	autumn	21	8 (38.1)	1.000
12	winter	27	9 (33.3)	0.683

Table 2:

In this table, all significant results from the univariate logistic regression model with breed always included as a potential confounder (p-value, OR and confidence limits) were shown grouped in different risk factor groups. Candidates for the multivariable (MV) model were selected. In order to avoid problems with collinearity in the final model, the association between candidate factors was assessed within topic groups (a) breeding conditions, (b) environment, (c) housing and (d) feeding using a cross tabulation and chi-square test. Factors within those groups that were significantly associated were either combined or one was excluded from further analysis

Potential risk factor	Comparison categories	p-value	OR ¹	LCL ²	UCL ³	Candidates for MV model	Information about the selection of the candidates
1. Date of birth							
a. Season (Baseline: autumn)	summer	0.058	0.556	0.304	1.019	-	excluded; resumed in factor 1b
	spring	0.320	0.737	0.403	1.346		
	winter	0.618	0.853	0.456	1.594		
b. Warm months (BL: spring/summer)	autumn/winter	0.091	1.440	0.944	2.196	x	included; summary of factor 1a
2. Breeding conditions							
a. Where kept during puppyhood (BL: house)	shed	0.003	22.565	2.849	178.714	-	excluded; resumed in factor 2b
	kennel	0.701	0.900	0.526	1.541		
	kennel and house	0.134	0.542	0.244	1.208		
	others	0.903	1.086	0.291	4.043		
b. Where kept during puppyhood (BL: all others)	shed	0.002	24.882	3.202	193.380	x	included; summary of factor 2a
c. Age at adoption (BL: < 8 weeks)	8-12 weeks	< 0.001	5.651	2.287	13.964	x	included; no correlation to other factors
	> 12 weeks	0.056	2.682	0.976	7.372		
d. Vaccinating status before adoption (BL: yes)	no	0.003	0.274	0.118	0.640	-	excluded; resumed in 2f
e. Deworming status before adoption (BL: yes)	no	0.010	0.397	0.196	0.804	-	excluded; resumed in 2f
f. Combination vacc AND deworming (BL: yes)	no	0.023	0.461	0.237	0.897	x	included; summary of 2d and 2e
3. Surroundings							
a. Environment (BL: rural)	urban	< 0.001	3.582	2.205	5.818	x	included; correlated to factors 3b, 3d, 3f and 3g
b. Contact with ruminants (BL: yes)	no	0.017	1.847	1.114	3.062	-	excluded; correlated to factor 3a
c. Contact with horses (BL: yes)	no	0.105	1.918	0.873	4.214	x	included; no correlation to other factors
d. Home with garden (BL: yes)	no	0.002	2.418	1.392	4.201	-	excluded; correlated to factor 3a
e. Walking in the forest (BL: yes)	no	0.006	2.465	1.288	4.717	x	included; no correlation to other factors
f. Walking through the fields (BL: yes)	no	0.061	1.705	0.975	2.982	-	excluded; correlated to factor 3a
g. Walking in a town park (BL: yes)	no	0.073	0.551	0.287	1.058	-	excluded; correlated to factor 3a
4. Housing conditions							
a. Wood-fired heating system (BL: yes)	no	0.007	2.123	1.228	3.672	x	included; no correlation to other factors
b. Parquet floor (BL: others)	yes	0.045	1.555	1.010	2.393	x	included; no correlation to other factors
c. Plants (BL: no or some)	many	0.042	0.429	0.189	0.969	x	included; no correlation to other factors
d. Dog basket (BL: yes)	no	< 0.001	0.418	0.255	0.686	x	included; no correlation to other factors
e. Dog pad (BL: yes)	no	< 0.001	2.362	1.400	3.984	x	included; no correlation to other factors
f. Living with other dogs (BL: yes)	no	< 0.001	2.266	1.400	3.667	-	excluded; resumed in factor 4h
g. Living with cats (BL: yes)	no	0.016	1.697	1.102	2.611	-	excluded; resumed in factor 4h
h. Living with dogs OR cats (BL: yes)	no	< 0.001	2.338	1.509	3.622	x	included; summary of factors 4f and 4g
i. Mold problems at home (BL: yes)	no	0.031	2.448	1.084	5.524	x	included; no correlation to other factors
j. Washing the dog (BL: yes)	no	0.004	0.525	0.339	0.813	-	excluded; correlated to factor 4k
k. Washing the dog (BL: no or less than once a month)	once per week or more	0.071	1.875	0.948	3.705	x	included; correlated to factor 4j
	less than once per week	0.004	6.865	1.871	25.193		
5. Feeding							
a. Food (BL: other / multiple feeds)	dry food	0.120	0.692	0.435	1.100	-	excluded; resumed in factor 5b
	wet food	0.970	0.984	0.427	2.267		
	home cooked	0.351	1.708	0.555	5.252		
b. Food (BL: dry food)	all others	0.055	0.662	0.434	1.009	x	included; summary of factor 5a
c. Oil supplementation (BL: yes)	no	0.015	0.374	0.169	0.826	x	included; no correlation to other factors

1: odds ratio

2: lower confidence level

3: upper confidence level

Table 3:

All remaining candidates were offered to an automatic forward selection process of the multivariable logistic regression analysis until 10 variables (including intercept) were selected in decreasing order of significance. Subsequently, non significant variables (p-value < 0.05) were manually in a stepwise elimination process. In a final step, breed was forced into the model to correct for any potential confounding effect, the parameter estimates of those factors remaining in the final model expressed as odds ratios and 95% confidence intervals.

Risk factor	Comparison categories	p-value	OR ¹	LCL ²	UCL ³
Breeding conditions					
Where during puppyhood (Baseline: others)	shed	0.006	19.60	2.37	162.03
Age at adoption (BL: < 8 weeks)	8-12 weeks	0.003	4.89	1.69	14.12
	> 12 weeks	0.105	2.86	0.80	10.17
Surroundings					
Environment (BL: rural)	urban	0.002	2.67	1.45	4.92
Walking in the forest (BL: yes)	no	0.033	2.52	1.08	5.90
Housing conditions					
Living with other dogs OR cats (BL: yes)	no	0.020	1.95	1.11	3.43
Washing the dog (BL: no or less than once a month)	once per week or more	0.011	21.47	2.05	225.31
	less than once per week	0.462	1.35	0.61	2.97

* corrected for the potentially confounding effect of breed

Possible interactions were not tested due to limited number of observations in the final model

1: odds ratio

2: lower confidence level

3: upper confidence level

Appendix:

The questions and possible answers of the questionnaire used in the statistical analysis.

Question	Possible answers
Date of birth	Day, month and year
In which season is the dog born?	In spring (months 3-5), summer (months 6-8), autums (month 9-11) or winter (months 12-2)
In which residential area does the owner live with the dog?	Rural, urban, both (rural and urban) or suburban
Is the home of the owner beyond 1000 meters above sea level?	Yes or no
Are there any lakes, rivers or streams in the surrounding area?	Yes or no
Is there a forest in the surrounding area?	Yes or no
Are there other animals in the surrounding area?	Dogs/cats, birds, ruminants, horses, rodents (including rabbits) or others
Does the owner have a garden?	Yes or no
Where does the owner prefer to walk the dog?	In the forest, in the fields, in the city park or other areas
Where does the dog live?	House/flat, kennel or elsewhere
Where does the dog stay during the day?	Indoor, outdoor or both
How is the house/flat heated?	Wood-fired heat, oil-fired heat, filament heat, gas-fired heat or any other heat
Was the domicile built after 1970?	Yes or no
Which kind of floor is predominant in the house/flat?	Carpet > wooden floor > flagged floor
How many plants are there in the house/flat?	A lot of plants, some plants or no plants
How often does the owner vacuum?	We grouped the answers in: 1-3 times / week, more than 3 times / week, less than 1 time / week
Does the owner use a special Hoover for allergic people?	Yes or no
Does the owner smoke in the residence?	Yes or no
In which room does the dog usually stay?	In the owners bedroom, living room, hallway, office or elsewhere
Where does the dog usually lie or rest?	In a dog basket, on a dog pad, in a bed or on the sofa or elsewhere
Are there any other animals/pets in the same household?	Yes or no, if yes, list other pet dogs, cats, rodents (including rabbits) or birds
Are there or were there any mold problems in the residence?	Yes or no
Does the owner regularly use a humidifier?	Yes or no
Does the owner regularly use an air freshener?	Yes or no
Does the dog regularly swim in water?	Yes or no
Does the owner bathe the dog at home?	With shampoo, only with water or no bathing
How often does the owner bathe the dog?	We grouped the answers in: every week, once a month or less than once a month
Which kind of food does the dog normally eat?	We grouped the answers in: dry food, wet food, home cooked or a combination
Does the dog regularly eat leftover food?	Yes or no
Does the dog regularly eat treats?	Yes or no
Does the dog regularly eat garbage (also faeces, carcass)?	Yes or no
Does the dog receive any food supplement?	We grouped the answers in: vitamins, trace elements, oil and others
What kind of material is the dog's food bowl made of?	Plastic > metal > other (glass or ceramic)
Is the dog regularly vaccinated?	Yes or no
Is the dog regularly dewormed? How often?	We grouped the answers in: Twice a year or more, less than twice a year
Where does the dog stay while the owner goes on holiday?	At home, at another place, in a shelter, he accompanies the owner on holiday
Has the dog ever vacated Switzerland (Germany)?	We grouped the answers in: Mediterranean, Europe exclusively Mediterranean, tropics
Where does the dog spend its time during the day?	At home, at another place or at your job
Was the dog imported?	Yes or no
Which was the breeder's country of origin?	Rural, urban or both (rural and urban)
What type of place did the original breeder female dog live in?	House/flat, kennel, shed or others
How old was the dog when it was adopted by the current owner?	We grouped the answers in: between 8 and 12 weeks, younger than 8 weeks, older than 12 weeks
Had the dog been vaccinated and/or dewormed when he was adopted by the owner?	Vaccinated, dewormed, both, nothing
When it was a puppy, what type of dog food did the puppy eat while he stayed with the breeder?	We grouped the answers in: dry food, wet food, home cooked or multiple
When it was a puppy, what did the dog eat when he living with the owner?	We grouped the answers in: dry food, wet food, home cooked or multiple
Has the dog ever had fleas or mites?	Yes or no

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3. Curriculum vitae

Name	Sabrina Rita Meury
Geburtsdatum	26. Dezember 1981
Geburtsort	Laufen BL
Nationalität	Schweizerin
Heimatort	Blauen BL
1988 – 1992	Primarschule Blauen
1992 – 1994	Sekundarschule Zwingen
1994 - 2001	Gymnasium Laufen, Maturität Typus B
2001 – 2007	Studium der Veterinärmedizin an der Universität Zürich
November 2007	Staatsexamen an der Universität Zürich
2002	Aushilfe Tierpflegerin, RCC Itingen
2005 – 2007	Tierpflegerin Spätdienst, Kleintierklinik, Tierspital Zürich
2008 - 2009	Klinische Dissertation an der Klinik für Kleintiermedizin der Vetsuisse Fakultät, Universität Zürich
2010	Betreuung e-learning Projekt für Studierende der Vetsuisse Fakultät Zürich und Bern

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